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Metabolic and Nutritional Features in Adult Celiac Patients

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Key Words
Celiac disease · Energy expenditure · Fat mass · Fat-free mass · Ghrelin · Gluten-free diet · Leptin

Abstract
Celiac disease (CD) is a chronic immune-mediated gluten-dependent enteropathy induced by ingestion of gluten-containing products, characterized by intestinal malabsorption and subtotal or total atrophy of intestinal villi, which improves after gluten-free diet (GFD). Untreated patients affected by the classic form of CD are at high risk of malnutrition, but an impairment of nutritional status is frequently reported also in patients with the subclinical form of the disease. Strict adherence to a GFD greatly improves nutritional status, inducing an increase in fat and bone compartments, but does not completely normalize body composition. A lack of improvement in nutritional status may identify incomplete adherence to GFD treatment. Evidence has shown lower body weights and lower fat mass and fat-free mass contents in CD patients. Untreated CD patients oxidize more carbohydrates as energy substrate compared to treated subjects. In addition, circulating ghrelin concentration was reduced after GFD treatment as a possible consequence of body composition improvement, while leptin did not correlate with the changes in body composition and substrate oxidation in patients with CD. A significant correlation was reported between ghrelin and the degree of severity of intestinal mucosal lesions. CD patients might show an alteration in lipid metabolism, i.e. low serum total and high-density lipoprotein-cholesterol as a consequence of lipid malabsorption and decreased intake. In conclusion, weight loss and nutritional deficiencies are relevant clinical features in CD. Thus, an early and accurate evaluation of nutritional status and energy metabolism represents a fundamental tool in the management of CD patients.

Introduction

Celiac disease (CD) is a chronic immune-mediated gluten-dependent enteropathy induced by ingestion of gluten-containing products and characterized by intestinal malabsorption and subtotal or total atrophy of intestinal villi, which improves after gluten-free diet (GFD) [1].

The prevalence of CD among the general population is reported to be as high as 1% [2], but this number is likely supposed to increase in the future decades. While a mass screening of the general population seems to be impractical, the identification of the population at high risk of developing CD to be screened specifically should lead to early diagnosis and a reduced risk of complications.

CD can be diagnosed in early childhood with classical symptoms, such as diarrhea and malabsorption, but also

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later in life and in adults presenting with a wider spectrum of symptoms than in children [3]. Approximately 50% of adult patients do not have clinically significant diarrhea [4], but only show weight loss and nutritional deficiencies, with consequently iron-deficiency anemia (now the most common clinical presentation in adults with CD) or macrocytic anemia due to folate deficiency, calcium, vitamin D and vitamin K deficiencies [4, 5]. Strict adherence to a GFD was reported to greatly improve nutritional status, essentially because of an increase in fat and bone compartments [5], while it is not able to completely normalize body composition. In addition, a lack of improvement in nutritional status may help in identifying an incomplete adherence to GFD treatment [6]. Thus an early identification of nutritional deficiencies may play a crucial role in preventing malnutrition-related complications and improving patients' quality of life [5]. Moreover, several and increasing extraintestinal clinical manifestations have been described in CD, such as bone fractures, infertility, neurologic, affective and psychiatric syndromes, skin manifestations, and autoimmune diseases, including type 1 diabetes and thyroid and/or liver diseases [4, 7–9].

In this review, we will analyze the most important and recent data on nutritional and metabolic features in CD patients, the related implications, and the effects of the GFD on these variables.

Clinical and Nutritional Features

Untreated patients affected by the classic form of CD, characterized by diarrhea, abdominal pain, and weight loss, are at high risk of malnutrition because of nutrient malabsorption secondary to intestinal atrophy. Consequently, nutritional deficiencies should be screened in CD patients, such as iron-deficiency anemia and fat-soluble vitamin deficiencies; vitamin deficiencies may aggravate retinopathy (vitamin A), systemic and peripheral neuropathy (vitamins B_{12} and E), complications of pregnancy (iron-deficiency anemia and folic acid deficiency), dental disease, limited joint mobility, osteopenia, and osteoporosis (vitamin D) [10]. Deficient intake and absorption of vitamin D and calcium, and the development of secondary hyperparathyroidism, should be present in patients with osteoporosis [11], and several studies have shown that osteopenia occurs in adult patients with CD and that a GFD can improve, if not normalize, bone mineral density [12–14].

As far as hydrosoluble vitamin deficiencies are concerned, according to Hallert et al. [15], CD patients following a GFD presented poorer vitamin status for folate and vitamins B_6 and B_{12}, even when taking nutrient supplements. Although vitamin B_{12} deficiency is not unusual in CD, pernicious anemia is considered uncommon [16, 17], while recovery from iron-deficiency anemia is possible with a GFD alone [18, 19].

Treatment with life-long GFD causes a marked improvement or a complete restoration of the intestinal mucosa, while recent evidence suggests that the nutritional deficiencies do not completely normalize after GFD [5, 6, 20]. Consequently, an early identification of nutritional deficiencies may play a crucial role in preventing malnutrition-related complications and improving patients' quality of life [5]; moreover, a lack of improvement in nutritional status may help in identifying an incomplete adherence to GFD treatment [6]. Moreover, CD may be associated to lactase deficiency, with consequent lactose intolerance. In order to reduce gastrointestinal symptoms linked to lactose malabsorption, untreated CD patients often reduce the intake of lactose-containing products that are frequently energy-dense food items. A possible daily caloric impairment could thus take place. Recently it has been shown that lactase deficiency seems to be the only manifestation of CD [21].

Finally, peculiar clinical and nutritional assessment could be present in CD patients with type 1 diabetes. In fact, the complications of type 1 diabetes can be exacerbated by nutritional deficiencies [10]; moreover, unexplained hypoglycemia with a reduction in insulin requirements should suggest to investigate for an undiagnosed CD [22]. On the other hand, in CD patients with associated type 1 diabetes CD, an acute hyperglycemia and a steady rise in hemoglobin A1c could occur with the initiation of a GFD, due to intestinal healing and better absorption [10].

Assessment of Body Composition, Energy Expenditure and Substrate Oxidation

In order to perform a correct evaluation of nutritional status and metabolic requirements it should be necessary to measure body weight components, i.e. fat mass (FM) and fat-free mass (FFM), total body water and to evaluate energy expenditure and nutrient utilization. Body composition can be assessed either by simple and easy-to-perform methods, such as anthropometry, skinfold thickness and biochemical measurements or by very sophisti-

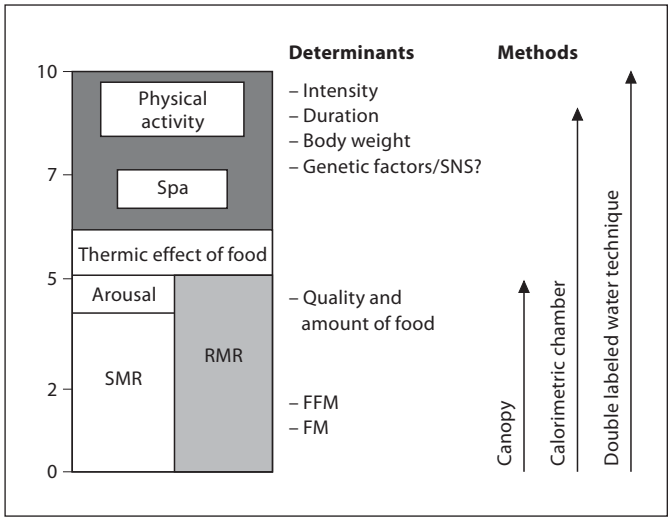

Fig. 1. Components of total energy expenditure in humans.

cated techniques, such as computed tomography and magnetic resonance imaging. These latest are also used to measure the visceral fat depots, by using a single scan at the lumbar level.

Very expensive techniques for body composition measurement such as isotopic dilution into water compartments or adipose cells, neutron activation analysis, computed tomography and magnetic resonance imaging need well-trained staff and are so far performed only in highly specialized centers.

The most commonly used techniques to assess body composition in clinical practice are:

Anthropometry and skinfold thickness measurement: Determination of body weight, height, body mass index (BMI), computed as the ratio between body weight (kg) and height (m^2). BMI values between 18.5 and 24.9 kg/m^2 indicate a normal weight condition, while values <18.5 or >24.9 indicate a condition of underweight up to malnutrition or overweight up to severe obesity, respectively. Measurement of waist circumference significantly correlates with increased risk of developing cardiovascular and metabolic diseases. Body fat and density can also be indirectly determined by skinfold thickness taken at the four standard sites: biceps, triceps subscapular and sacroiliac.

Bioimpedance analysis: A rapid and simple method for measuring the different body compartments; it is based on the principle that conductance of a tissue or of the entire body correlates with the mean water and electrolytes content and thus the conductivity is greater in the FFM and proportional to it [23].

Dual-energy x-ray absorptiometry (DXA): DXA is based on the attenuation that an x-ray or a photon ray receives when passing through a human body. The 'total body' densitometer used to measure bone mineral density should be used also to assess the amount of body fat and FFM. DXA is a very precise and reproducible technique for measuring soft tissues and in particular FM [24].

As far as the assessment of energy requirements is concerned, total energy expenditure measured over 24 h can be determined using sophisticated and expensive techniques, such as the double labeled water technique and the calorimetric chamber or in clinical practice by portable indirect calorimeters. The total energy expenditure is made of different components, as shown in figure 1, and open-circuit indirect calorimetry is the most commonly used technique to assess resting metabolic rate and diet-induced thermogenesis; this procedure, by means of gaseous exchange and 24-hour urinary nitrogen excretion measurements, allows to determine energy expenditure and substrate utilization, providing the respiratory quotient value, which is computed as the ratio between CO_2 excretion and O_2 production by the subjects [25].

Body Composition and Energy Expenditure in CD

Ample evidence has shown lower body weights and lower FM and FFM contents in both untreated and treated CD patients than in control subjects [6, 20, 26–28]. In particular, confirming our previous case-control study [20], our laboratory performed, for the first time, a longitudinal study, showing that untreated patients of both sexes and treated male patients had FFM values that were significantly higher than those of control subjects; moreover, there was a significant increase in body weight and FM after the GFD treatment [5]. As a consequence of the larger decrease in FM than in FFM in male CD patients after the GFD treatment, these patients had very high % FFM values. Moreover, higher resting metabolic rate values were found in both CD groups than in control subjects [5]. From this point of view, the increased rate of intestinal mucosa protein synthesis and of renewal and migration of epithelial cells reported in untreated CD [29, 30] could be considered partially responsible for the increased resting metabolic rates in these patients in addition to the inflammatory nature of the disease [5]. Untreated CD patients oxidize more carbohydrates, as shown by the higher npRQ value in untreated patients than in control subjects and treated patients [5], and this

aspect is related to the necessity to provide energy to the organism [5, 20, 31], considering the chronic lipid malabsorption, and as also demonstrated by the not different total daily energy intake among control group and CD patients, both before and after the GFD treatment [5, 20, 32].

Lipid Metabolism in CD

With regard to the lipid profile in CD patients, an alteration in lipid metabolism can easily occur in disorders of the small bowel mucosa, essentially as a consequence of lipid malabsorption and decreased intake [5]. In this connection, presence of low-serum high-density lipoprotein-cholesterol (HDL-C) concentration has been identified as an early sign of CD [33]. This feature could be explained by the reduction in cholesterol-transporting lipoproteins, induced by the decreased lipid absorption and the decreased apolipoprotein (Apo)-A1. The last one is produced at the small bowel level and represents the main portion of HDL-C particles [33]. Accordingly, a significant increase in triglycerides, total cholesterol and HDL-C but not in low-density lipoprotein cholesterol (LDL-C) was found in CD patients after GFD by Brar et al. [34]. Since the HDL-C level represents one of the most relevant risk factors for cardiovascular diseases, the improvement in lipid profile after GFD suggested a decrease in cardiovascular risk in CD patients [34].

Hormones Regulating Energy Balance in CD

A great interest has been recently devoted to the interaction of new molecules which regulate body weight maintenance in both animals and humans, acting as signals between the peripheral organs and the hypothalamus [35]. Among these substances, leptin, which is secreted mainly by the adipocytes, was shown to increase energy expenditure, while decreasing energy intake in experimental animals and in humans [36]. Leptin production or presence of its receptors at different intestinal levels has been demonstrated [37].

An opposite role in the regulation of energy balance is played by ghrelin, a 28-amino-acid peptide produced by the enteroendocrine cells of the gastric mucosa and the intestine [38–41]. Ghrelin action is almost twofold, as it is the endogenous ligand for the GH secretagogue receptor and is able to increase food intake and reduce energy expenditure [40].

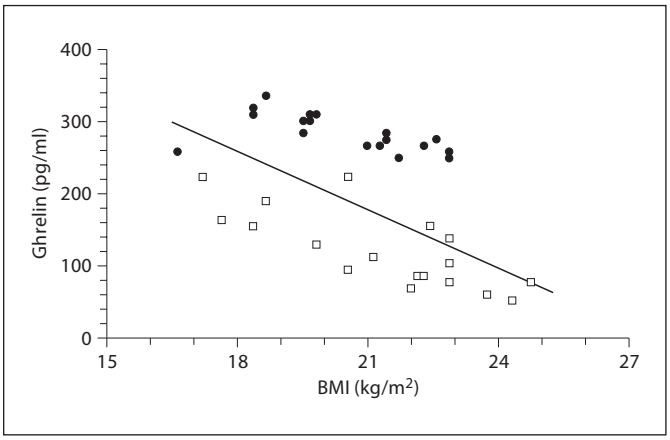

Fig. 2. Relationship between plasma ghrelin concentration and BMI in adult CD patients before (●) and after (□) GFD treatment ($r = -0.32$; $p < 0.01$) [modified from 42].

With regard to the possible action of these hormones in the metabolism of CD patients, our recent data have shown that while a circulating leptin concentration did not correlate with the changes in body composition and substrate oxidation, a low circulating ghrelin concentration is present in CD patients after GFD treatment and could be almost partially explained by the slight increase in body weight and FM (fig. 2) [42]. Taking into account that the role of insulin in regulating ghrelin secretion is largely debated [43], insulin levels were also evaluated in our patients. However, no correlation was found between ghrelin and insulin in either treated or untreated patients, nor was a difference found in plasma insulin concentration before and after GFD, suggesting that insulin does not play a pivotal role in regulating ghrelin secretion in CD.

Our data on ghrelin in CD patients are partially in contrast with those of Peracchi et al. [44], who reported a significant correlation between ghrelin and the degree of severity of intestinal mucosal lesions in patients with CD, representing evidence of the possible role of ghrelin in the inflammatory processes. The most relevant difference between our data and those of Peracchi et al. [44], showing a similar ghrelin concentration in treated patients and healthy subjects, is that we found a lower ghrelin concentration in treated CD patients compared to control subjects (109.2 ± 49.9 vs. 262.2 ± 30.0 pg/ml). This finding should be almost partially explained by differences in patients' characteristics, such as gender, duration of the disease, and age of onset before diagnosis.

A successive study by Lanzini et al. [45] showed elevated ghrelin levels in untreated celiac patients, apparently in contrast with the normal ghrelin levels found in our CD patients [42]. However, since both studies showed an increase in the BMI and a decrease in ghrelin levels after GFD in CD patients [42, 45], this discrepancy could be explained – at least in part – by the possible differences in choosing the control group. In particular, it should be underlined that our study considered only female CD patients and consequently only healthy female controls. On the contrary, in the subjects enrolled by Lanzini et al. [45], a discrepancy in gender distribution is present between CD patients (10 males and 34 females) and healthy controls (45 males and 8 females). A further comparison between the two studies is difficult to establish since in the study of Lanzini et al. [45] no data are reported about body composition (i.e. FM and FFM).

Further studies are warranted to better investigate the influence of other variables, such as GH secretion [46] and regional cerebral blood flow abnormalities [47], on ghrelin secretion in CD.

Conclusions

Weight loss and nutritional deficiencies represent relevant clinical features in CD, other than the possible presence of associated diseases with important metabolic implications, such as type 1 diabetes and thyroid and/or liver diseases. Nutritional alteration may be found not only in the classical form of CD, with the overt signs and symptoms of malabsorption, but even in the subclinical form of the disease. Thus, an accurate evaluation of body composition and energy metabolism may represent a tool for an early diagnosis.

Recent evidence has shown that nutritional deficiencies did not completely normalize after treatment with GFD [5]. In this respect, the early identification of nutritional deficiencies represents a primary aim also in the clinical management and prognosis of CD patients. Moreover, the application of molecular and hormonal studies in CD could allow a better clarification of the pathophysiology of malnutrition, also permitting to investigate the potential therapeutic role of some mediators (e.g. a possible orexigenic role of ghrelin) in clinical practice.

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